REMARKS

Status of the claims

Upon entry of these remarks, claims 85-91, 118-124 and 148-182 will be pending in this application. Claims 1, 17, 19, 26-84, 92-117, and 125-147 have been canceled without prejudice or disclaimer. Applicants' purpose in canceling these claims is solely to simplify, and therefore facilitate, prosecution of the instant application. Applicants assert that each of the canceled claims is fully enabled and satisfies the statutory requirements under 35 U.S.C. § 112. Applicants reserve the right to pursue the subject matter of the claims cancelled herein in one or more continuing applications.

Support for the newly added and amended claims is found throughout the specification as filed, and no new matter has been introduced.

Claims 85, 118, 148, and 158 have been amended to recite *antagonistic* antibodies (amendment indicated in italics). Support for claims directed to using antagonistic antibodies that specifically bind Neutrokine-alpha polypeptides to treat autoimmune disorders may be found, for example, on pages 20-21 and 333-337 of the specification as filed. Treatment of rheumatoid arthritis and systemic lupus erythematosus are specifically disclosed, for example, at pages 336-7 of the specification as filed.

Support for the antibodies used in the claimed methods can be found, for example, on pages 228-310 of the specification as filed. Support for claims directed to monoclonal and polyclonal antibodies and Fab fragments of antibodies can be found, for example, on pages 228-229 of the specification as filed. Support for claims directed to labeled antibodies, or antibodies conjugated to a therapeutic or cytotoxic agent can be found, for example, on pages 252-254 of the specification as filed. Thus, no new matter has been added by way of amendment.

Claims 148 and 158 have been amended to recite that the claimed Neutrokine-alpha polypeptide "modulates lymphocyte proliferation, *differentiation or survival*" (amendment indicated in italics). Support for these amendments may be found, for example, in the specification as filed at the third full paragraph on page 18, the paragraph spanning pages 46-47, the second paragraph on page 56, and the paragraph spanning pages 81-82, and Examples 6 and 7.

For the Examiner's convenience, a Clean Version of the Entire Set of Pending Claims (including amendments made herein) as allowed for under 37 C.F.R. §1.121(c)(3) is enclosed.

Substitute Specification

In accordance with the Examiner's request that Applicants check the specification for minor errors, Applicants provide herewith a substitute specification as well as a Version of the Substitute Specification with Markings to Show Changes Made.

The undersigned attorney of record hereby states under 37 C.F.R. §1.125(b)(1) that the substitute specification filed herewith contains no new matter. Each of the amendments to the specification are shown in boldfaced text in the Version of the Specification With Markings to Show Changes Made submitted herewith in which insertions are indicated by underlining and deletions are indicated by strikeout. The amendments either (1) correct grammatical and/or clerical errors (2) amend the specification to add SEQ ID NOs for sequences disclosed in the specification as filed, or (3) were made and entered previously (i.e., the amendments proposed in the Preliminary Amendment filed July 28, 2000 have been entered into the Substitute Specification).

Title

The Examiner objected to the title of the application alleging that it was not descriptive of the claimed invention. In accordance with the Examiner's suggestion, Applicants have amended the title to "Methods of Treatment Using Antibodies to Neutrokine-alpha." This amendment has been incorporated into the Substitute Specification submitted herewith.

Replacement Sequence Listing

The Substitute Sequence Listing submitted herewith has been amended to bring the Sequence Listing into compliance with the 37 C.F.R. §1.821- §1.825. Briefly the amendments to the Sequence Listing include: (a) amendment of the header information to correctly identify the present application and the applications to which it claims priority; (b) amendment of the header information preceding primer sequences (SEQ ID NOS: 10-17, 24-26, 31-36 and 39-42) to bring them into the appropriate format; (c) amendments to SEQ ID NO:38 to make the Sequence Listing correctly reflect SEQ ID NO:38 as defined in the specification, for example at pages 129-130; and (d) to add SEQ ID NOS:39-42 which correspond to sequences disclosed in the specification at page 420, lines 2-3 and

page 421, lines 15-16. Each of the amendments is supported by the specification as originally filed and no new matter has been introduced.

Rejections under 35 U.S.C. §112, first paragraph

Claims 26-164 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement and written description.

A. Enablement Rejection

The Examiner rejected claims 26-164 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement stating that:

> There are two major aspects of total lack of enablement addressed in this rejection:
> (a) treatment of immune system disease, or disorder, or autoimmune disease, or disorder, or immunodeficiency using antibodies that specifically bind to 'full length neutrokine-α of SEQ ID No.2; and
> (b) use of antibodies that specifically bind to full length polypeptide of SEQ ID No. 2 or fragments, derivatives, portions or fusion peptides, or N-, C-, N- and C- terminal deletion mutants of neutrokine-α of SEQ ID No. 2 for any treatment of immune system disease, or disorder, or autoimmune diseases, or disorder, or immunodeficiency.
>
> *See,* Paper No. 8, top of page 4.

Preliminarily, Applicants bring to the Examiner's attention that Applicants have cancelled:

- claims 1, 17, 19, 125-130;
- claims 26-63 and 131-164 drawn to methods of treating an immune system disease or disorder using antibodies of the invention; and
- claims 64-84 drawn to methods of treating an autoimmune disease or disorder using antibodies of the invention.

Applicants' purpose in canceling these claims is solely to simplify, and therefore facilitate, prosecution of the instant application. Applicants assert that each of the cancelled claims is fully enabled and satisfies the statutory requirements under 35 U.S.C. § 112. Applicants reserve the right to pursue the subject matter of the claims cancelled herein in one or more continuing applications.

As Applicants have cancelled the above claims, Applicants will only rebut the present rejections insofar as they apply to the pending claims.

Neutrokine-alpha antibodies may be used to treat autoimmune disease.

The Examiner contends that "it is not feasible for one of skill in the art to treat unnamed...autoimmune disease, or disorder...as recited in the instant claims." (Paper No. 8, page 7, lines 3-4).

Applicants respectfully disagree.

First, Applicants note that increased Neutrokine-alpha levels in serum and/or synovial fluid correlate with murine models of autoimmunity[1] as well as with human autoimmune syndromes, including immune based rheumatic diseases including Rheumatoid Arthritis[2], Systemic Lupus Erythematosus[3], and Sjögren's Syndrome[4]. The observation that elevated levels of Neutrokine-alpha are associated with several human and mouse autoimmune syndromes has led those skilled in the art to state that Neutrokine-alpha blocking agents hold great promise in the treatment of autoimmunity[5, 1-4]. Further, treatment of autoimmune mice with a Neutrokine-alpha blocking agent is known to alleviate the symptoms of autoimmune disease[6]. Together, these facts demonstrate that it is feasible for one of skill in the art to treat autoimmune diseases with Neutrokine-alpha blocking agents such as the antagonistic antibodies used according to the claimed methods.

The Examiner also finds the specification lacking in enablement because there is no guidance as to the selection of patient population or to what are the symptoms that should be alleviated. Applicants respectfully disagree with this basis of the rejection.

The M.P.E.P. states in § 2164.08:

> The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.

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[1] Gross et al., *Nature* (2002) 404:995-999 cited as reference A51 submitted August 20, 2001.
[2] Cheema et al., *Arthritis Rheum.* (2001) 44:1313-1319 cited as reference B5 submitted herewith. Neutrokine-alpha is also known as B Lymphocyte Stimulator.
[3] Zhang et al., *Journal of Immunology* (2001) 166:6-10 cited as reference A69 submitted August 20, 2001.
[4] Marriette et al., 65th Annual American College of Rheumatology Scientific Meeting. Nov. 2001 cited as reference B6 submitted herewith.
[5] Vaux et al., *The Journal of Clinical Investigation* (2002) 109:59-68 cited as reference B8 submitted herewith. Neutrokine-alpha is also known as BAFF.
[6] Gross et al., *Nature* (2002) 404:995-999 cited as reference A51 submitted August 20, 2001.

Applicants submit that such information regarding the selection of a patient population and the alleviation of symptoms is well known to those skilled in the relevant arts. For example, Rheumatoid arthritis (RA) is a chronic disease of autoimmune origin that causes pain, stiffness, swelling and loss of function in the joints and inflammation in other body organs. The RA classification criteria established by the American College of Rheumatology include symptoms of prolonged morning stiffness in the joints, soft tissue swelling or fluid in joint areas, characteristic nodules under the skin, joint erosions apparent on X-ray tests, and elevated levels of serum antibodies known as rheumatoid factor[7]. Accordingly, one of skill in the art would be able to identify the RA patient population and know that treatment of RA should result in reduction or elimination of one or more of the above described symptoms of RA. Similar arguments may be made for other autoimmune diseases such as Systemic Lupus Erythematosus and Sjögren's Syndrome.

In summary, Applicants have shown that treatment of members of the *class* of autoimmune diseases using anti-Neutrokine-alpha antibodies of the invention is feasible and that one of skill in the art can clearly identify patients with autoimmune disease and determine if treatment has alleviated their symptoms without undue experimentation. Accordingly, Applicants respectfully request that this aspect of the rejection (subpart (a) quoted above) under 35 U.S.C. §112, first paragraph, be withdrawn.

The antibodies of the invention are fully enabled

The Examiner contends that the "[i]nstant specification fails to provide what is the specificity of the numerous proposed antibodies to the contemplated antigenic/epitopic regions" and that

> '[i]n spite of the numerous contemplated epitope bearing regions of SEQ ID NO.2 and the corresponding antibodies, the specification fails to provide information on the comparison of such antibodies to full length polypeptide to those directed to potions of SEQ ID NO.2 for responses such as (a) inhibition of B-lymphocyte proliferation, (b) neutralization of ligand receptor interaction, or (c) a table of immunogens and the titers of the antibodies generated in binding to the full length polypeptide or the said fragments. (Paper No. 8, page 7).

[7] Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-324 cited as reference B9 submitted herewith

Preliminarily, Applicants as discussed above, claims 1, 17, 19, 26-63, 64-84, 125-130, 131-147 have been cancelled without prejudice or disclaimer, solely in the interest of facilitating prosecution.

Applicants disagree with this basis for the rejection under 35 U.S.C. §112, first paragraph. Applicants point out that in the current context, there is no requirement that an antibody used according to the claimed methods be distinguished from any other antibody used according to the claimed methods. Accordingly, it is irrelevant whether the specification describes how each antibody that may be used according to the claimed methods is different from the other.

Additionally, Applicants direct the Examiner's attention to Examples 6 and 7 of the specification in which assays for determining if Neutrokine-alpha binds to cells expressing Neutrokine-alpha receptor (e.g., IM9 cells) and if Neutrokine alpha can act to stimulate proliferation of B cells. These assays can easily be modified by one of skill in the art to determine if an anti-Neutrokine-alpha antibody antagonizes Neutrokine-alpha/Neutrokine-alpha receptor interactions and/or Neutrokine-alpha mediated stimulation of B cell proliferation. These assays enable one of skill in art to determine, for themselves, without undue experimentation if antibodies used in the claimed methods have the properties of inhibiting Neutrokine-alpha/Neutrokine-alpha receptor interaction or inhibiting Neutrokine alpha induced B cell activation, survival or proliferation.

Applicants also remind the Examiner that the enablement requirement of 35 U.S.C. § 112, first paragraph requires nothing more than objective enablement. A specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of § 112, unless there is reason to doubt the objective truth or accuracy of the statements relied upon therein for enabling support. *Staehelin v Secher*, 24 USPQ2d 1513, 1516 (B.P.A.I. 1992), *In re Marzocchi*, 169 USPQ 367 (C.C.P.A. 1971); *In re Brana* 34 USPQ2d 1437, 1441 (Fed. Cir. 1995).

Furthermore, the Federal Circuit has acknowledged in *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988) and in *Hybritech Incorporated v. Monoclonal Antibodies Inc.,* 231 USPQ 81 (Fed. Cir. 1986) that making and characterizing antibodies is routine to one of skill in the art. Thus, Applicants' specification does not fail to be enabling because it is not laden with experimental details that could easily and routinely be generated by one of skill in the art. In view of the foregoing, Applicants respectfully request that this aspect of the rejection (subpart (b) in the passage quoted above) under 35 U.S.C. §112, first paragraph, be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present Amendment be entered and made of record in the present application.

In view of the foregoing remarks, applicants believe that this application is now in condition for allowance. An early Notice of Allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to Deposit Account No. 08-3425.

Respectfully submitted,

Date: May 3, 2007

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KKH/MS/vsr

Via Hand Delivery May 3, 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: **Yu, et al.**

Application Number: 09/589,288 Group Art Unit: 1646

Filed: June 8, 2000 Examiner: Prasad, S.

Title: **Methods of Treatment Using Antibodies to Neutrokine-alpha (as amended)** Atty. Docket No. PF343P3C5

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amendments are shown in bold with insertions indicated with underlining and deletions indicated by strikeout.

In the Specification:

The current Specification has been replaced with the Substitute Specification filed herewith.

In the Sequence Listing:

The current Sequence Listing has been replaced with the Substitute Sequence Listing submitted herewith.

***In the Claims*:**

Claims 1, 17, 19, 26-84, 92-117, and 125-147 have been cancelled without prejudice.

New claims 165 to 182 have been added.

Claims 85, 118, 148, and 158 have been replaced with the following amended claims:

85. (Once Amended) A method of treating an autoimmune system disease or disorder comprising administering to an individual, a therapeutically effective amount of an **antagonistic** antibody or portion thereof that specifically binds a protein consisting of an amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

118. (Once Amended) A method of treating rheumatoid arthritis comprising administering to an individual, a therapeutically effective amount of an **antagonistic** antibody or portion thereof that specifically binds a protein consisting of the amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

148. (Once Amended) A method of inhibiting leukocyte ~~activation or~~ proliferation**, differentiation or survival** comprising administering to an individual, a therapeutically effective amount of an **antagonistic** antibody or portion thereof that specifically binds a protein consisting of an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274 to 284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284.

158. (Once Amended) A method of inhibiting leukocyte ~~activation or~~ proliferation**, differentiation or survival** comprising administering to an individual, a therapeutically effective amount of an **antagonistic** antibody or portion thereof that specifically binds a protein consisting of an amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.